Universidade de Lisboa

Faculdade de Farmácia

Nanoparticles as Ocular Drug Delivery Systems

Diogo Santos Capítulo

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

As doenças oculares como o glaucoma, degeneração macular relacionada com a idade, olho seco, entre outras, têm vindo a apresentar uma prevalência cada vez maior na população mundial e prevê-se um aumento destes números no futuro. Contudo, as terapêuticas convencionais continuam a apresentar muitas limitações devido não só às suas formulações, mas também às características anatómicas e fisiológicas do olho, um órgão único com muitas barreiras à administração de fármacos. Enquanto as gotas apresentam uma grande conveniência, elevada adesão à terapêutica por parte dos doentes e baixos custos económicos, mas uma baixa biodisponibilidade, as injeções conseguem ultrapassar mais facilmente as barreiras oculares, tendo maior biodisponibilidade, mas têm como inconvenientes uma baixa adesão à terapêutica, custos mais elevados e o facto de poderem danificar o globo ocular por serem métodos invasivos. Para solucionar estes problemas que acabam por ter um grande impacto no tratamento das doenças oculares, nos últimos anos tem-se vindo a investigar mais e mais o papel das nanopartículas como as nanomicelas, "nanowafers", niossomas, lipossomas, micro-agulhas, dendrímeros e nanopartículas constituídas por polímeros como quitosano, ácido hialurónico, PEG, entre outros nas doenças oculares e a sua incorporação nas formulações convencionais a fim de aumentar a sua biodisponibilidade, diminuir a toxicidade ou potenciais efeitos adversos que advêm do próprio processo de administração de fármacos como por exemplo as injeções intravitreas e, como principal objetivo, aumentar a eficácia destas terapêuticas. Estas tecnologias têm alcançado resultados promissores devido à sua capacidade de encapsulamento de fármacos, elevada mucoadesão, que por sua vez leva a uma controlada e prolongada libertação do fármaco, a capacidade de penetrar nas camadas mais posteriores do olho e a biocompatibilidade que apresentam, prevenindo reações adversas. Mais recentemente, a inovação tem levado à combinação de várias nanopartículas para formar partículas híbridas que mostram melhores resultados comparativamente ao uso isolado de cada nanopartícula.

Palavras-chave: Nanopartículas, olho, barreiras oculares, veiculação

Abstract

The prevalence of ocular diseases like glaucoma, age-related macular degeneration (AMD), dry eye, among others, has increased on a world-wide scale and it is expected to grow even further in the foreseeable future. However, conventional therapies continue to present several limitations due to not only the nature of their formulations but also the eye's anatomical and physiological characteristics, it being an unique organ with many barriers that affect drug delivery. While eye drops present themselves as a highly convenient method with low economic costs and a high patient compliance but with low bioavailability, eye injections can achieve high concentrations in the ocular globe but present lower patient compliance, higher costs and also bare the risk of damaging the ocular globe due to their invasive nature. In recent years, there has been an increase in the investigation surrounding nanoparticles as a way to overcome these problems that end up having a great impact on the treatment of ocular diseases overall. Nanoparticles such as nanomicelles, nanowafers, niosomes, liposomes, microneedles, dendrimers and nanoparticles made out of polymers like chitosan, hyaluronic acid, PEG, among others have been studied as systems to be incorporated in conventional therapies as a way to increase bioavailability, decrease toxicity or potential side effects deriving from more invasive methods such as intravitreal injections, and, in the end, as a way to increase therapeutic outcomes overall. These technologies have shown promising results due to their encapsulation characteristics, high mucoadhesion, that leads to a higher controlled release of the administered drug over a prolonged period of time, the ability to penetrate the inner layers of the ocular globe and high biocompatibility, which prevents adverse effects. More recently, innovation in this field has lead to the combination between different nanoparticles, achieving new hybrid particles that have shown better results compared to the usage of each nanoparticle type alone.

Key words: Nanoparticles, eye, ocular barriers, drug delivery

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Introduction

Over the past years, novel ocular drug delivery systems have been developed to tackle several problems that traditional formulations present such as low bioavailability but also to low patient compliance, especially when it comes to posterior ocular diseases (1). Due to the complexity of this organ, there are crucial characteristics that have to be taken into account such as the permanent washing of the eye by the tear fluid, that contributes to the drug removal and the anatomical and physiological barriers that often stop the drug to reach the affected site (2).

To tackle all these problems, several new formulations such as nanoparticles, liposomes, nanomicelles, microneedles, dendrimers, nanowafers and niosomes have recently been developed, bringing new strategies to assure better treatment for ocular pathologies.

In this article we will explore these new formulations, from the perspective of its importance overcoming ocular barriers and how are they changing or improving conventional formulations to reach better therapeutic outcomes.

Objectives

The objective of this study is to review the evolution of nanoparticles in the last years and how they present themselves as innovative and game changing technologies to improve ocular drug delivery by looking at their advantages and disadvantages. To be able to achieve any conclusions about nanoparticles in ocular drug delivery, a background investigation about the anatomical and physiological characteristics of the eye was made as well as a research about conventional ocular therapeutic routes and its advantages and disadvantages.

Anatomic and Physiological Characteristics of the Eye

The eye is an organ that due to being in an isolated position compared to other human organs, presents special characteristics such as specific physiological and anatomical barriers that aim to protect the eye from external aggressions. Because of this, the eye has to be observed in a different light compared to other organs in the human body. The eye is divided into an anterior and posterior part and ocular diseases are characterised based on these two segments. The anterior part is divided into the cornea, conjunctiva, iris, crystalline lens, ciliary body and aqueous humour whereas the

posterior part consists of the sclera, vitreous humour, retina, choroid and the Brunch's membrane (3).

Starting with the anterior part of the eye, the cornea is a very sensitive tissue positioned in the outer most part of the eye and consists of six layers: the epithelium, Bowman's membrane, stroma, Dua's Layer, Descemet's membrane and the endothelium. The epithelium is one of the main barriers for the drug passage to the eye due to being composed by multiple layers of epithelial cells that form tight junctions (3). This fact, together with the epithelium lipophilic nature, makes it one of the main barriers to drug penetration in the eye (90% to hydrophilic drugs and 10% to hydrophilic ones) (4). Drugs passage through this barrier is done both by passive diffusion (mainly for lipophilic) or through pores in the membrane (mainly for hydrophilic) and studies show that passive diffusion is the route through drugs usually enter the eye. Apart from the epithelium, only the stroma, a structure with a net shape configuration with hydrophilic nature that offers resistance to the passage of lipophilic drugs, and the endothelium, a thin membrane that offers some resistance to lipophilic drugs, represent barriers to drug delivery in the anterior part of the eye. Both Bowman's and Descemet's membrane offer no resistance to both hydrophilic and lipophilic drugs. Dua's layer functional role is yet to be determined (4,5).

On the posterior part of the eye, the sclera is a structure with hydrophobic nature, that can interfere with drug delivery due to being composed by collagen fibres (derived from the dura mater) that decrease the concentration of the drug that passes through and makes the drug distribution heterogeneous. The choroid is a structure that can be found between the retina and sclera and is composed of blood vessels that irrigates the back of the eye. These vessels have an important role in the clearance of drugs in the posterior segment of the eye and can pose one more barrier to achieve optimal drug concentrations. The vitreous humour is a gel-like fluid that is situated between the lens and the retina composed almost completely by water with a very small percentage of collagen fibrils, ions and hyaluronic acid. As the years go by, the fluidity of the vitreous humour increases, leading to health conditions. The retina is a multi-layered tissue that due to its sensitivity to light, generates impulses that go to the brain through sensory nerves. In this tissue, we have the blood-retina barrier that poses one more ocular barrier by acting in the systemic administered drugs and also drug clearance (5). Bruch's membrane, in the posterior segment of the eye, is explained ahead since it is an important ocular barrier.

The barriers to drug administration can be divided into static and dynamic and they are different in both the anterior and the posterior part of the eye.

In the anterior part, as static barriers, we have the cornea due to the characteristics of cornea's epithelium layers that offer resistance to drugs penetration in the eye. With a big role in this barrier effect, we have the tight junctions, that prevent a paracellular transport of ionic polar molecules, and the lipophilic nature of cornea's epithelium. Not only that, but the ionization state of molecules also plays an important role, especially in transcellular diffusion. Also, the stroma is a hydrophilic rate-limiting barrier that influence the absorption of lipid-soluble molecules. As the conjunctiva doesn't offer much resistance to molecules permeation, it allows paracellular, transcellular, active transport and passive diffusion transport of molecules to the inner parts of the eye. The blood-aqueous barrier is formed by the ciliary blood vessels, the non-pigmented cells of the ciliary epithelium and the endothelial cells of the iris. Limiting drug passage are tight junctions formed by this barrier and, on the other hand, it also limits by allowing a faster clearance of molecules. At last, we have the efflux pumps that are responsible for pumping out xenobiotics, reducing inner drug concentration. As for the dynamic barriers of the anterior segment, we have the tear drainage that leads to a faster elimination of drugs administered through the topical route. Despite the tear film being composed by many different substances, it is mucin that forms a protective hydrophilic layer that clears pathogens and debris from the eye. In addition to this, the fact that this tear film can be rapidly restored (2-3 minutes), can pose a problem for drug absorption through the eye (1). Since the conjunctiva is highly vascularized, we have the conjunctival blood and lymph flow as another dynamic barrier that ends up draining drugs administered topically in the precorneal pocket. The aqueous humour is an ocular fluid secreted by the epithelial of the ciliary body in the opposite direction of drug administration (i.e. from the outside to the inside of the eye) and because of that, the flow of drug entering the eye can collide with the aqueous humour flow, decreasing drug penetration. Hydrophilic drugs with a significant molecular weight are eliminated by the aqueous humour causing limited efficacy of drugs aimed at inner ocular targets.

Focusing now on the posterior segment ocular barriers, as static barriers we have the sclera, Bruch's membrane, the blood retinal barrier and efflux pumps and as dynamic barriers we have the choroid, a highly vascularised tissue. The sclera is a layer of the eye that limits the absorption of drugs with higher lipophilicity, weight and due to the negativity nature of membrane pores, it also interacts with exogenous molecules. The thickness of the sclera increases the more posterior it is, so the posterior sclera is very impermeable to the passage of drugs to the posterior part of the eye. The Bruch's membrane is deeply connected with the choroid and the retina because it's involved in nutrient's exchange between the retina and the blood and lymph vessels from the choroid. As the age advances, the thickness of this membrane also increases which

leads to an increase in the resistance to drug passage through this membrane. The blood retinal barrier has characteristic tight junctions in the more external part and in the more inner part the retinal capillary endothelial cells that lack fenestrations, limiting passive diffusion passage of drugs, restricting absorption to highly specific conditions and active transport pumps. In the posterior part of the eye, it is possible to also find efflux pumps that have the role of pumping out foreign molecules, dropping drug concentrations in the intracellular space, decreasing the efficacy (6). Lastly, as a dynamic barrier we have the blood and lymph vessels of the choroid that eliminate mostly lipophilic drugs to systemic circulation, decreasing drug concentrations to subtherapeutic levels. Studies have shown that this barrier does not significantly influence hydrophilic molecules elimination due to the fact that these molecules present a lower partition coefficient compared with lipophilic molecules (3,5,7–10).

Ocular Barriers and Conventional Therapy Routes

In the present days, there are three main routes of administration for drugs in the eye: topical administrations, injections and systemic administration.

The topical administration of eye drops is the most common therapeutic, especially for diseases that affect the anterior part of the eye, due to economic reasons, patient compliance, non-invasive and to the advantage of being self-administered. Despite all the advantages that carries, only one to seven per cent of drugs administered through this route reach its destination. The tear film is the first barrier eyedrops encounter when they contact with the ocular globe, as it was previously mentioned. Each eyedrop has an average of 39 (range 25-56 ,microliters) this volume ends up being washed up in just 15 to 30 seconds (1). This happens not only due to the tear film rapid restoration, but also because of the reflex blinking that happens when the eyedrop is administered. Since the cul-de-sac (include this in eye physiology) can only hold momentarily 30 (microliters), the exceeding volume is eliminated through the nasolacrimal channel (6). Also contributing to this fast elimination, we can mention the ocular physiological barriers such as the cornea and the conjunctiva. However, other ocular topical formulations are ocular suspensions that are characterised by having insoluble particles that are deposited in the precorneal cavity and having its drug bioavailability affected by the particle size, that will influence the absorption of the drug (11). In this category, we can also name ocular emulsions are also utilised as a viable formulation due to the lipophilic and aqueous nature that allows for both hydrophobic and lipophilic drugs to be dissolved. The most common emulsion is the O/W due to

causing low ocular irritation that can lead to better tolerability and compliance, but also higher drug bioavailability (11,12).

Eye injections are a therapeutic route that refers to intracameral, subconjunctival and intravitreal injections. It has the advantage of being able to reach high concentrations of the drug inside the eye and the drug delivery system is more straightforward than all other methods but since it is an invasive method, it can lead to some discomfort and cause other problems, connected with more invasive injections such as intravitreal injections, like retinal detachment, haemorrhage and discomfort for the patients (13). Intravitreal injections are administered directly into the vitreous cavity, resulting in high concentrations of the drug in the vitreous cavity and also in the retina. This route of administration is used to treat posterior ocular diseases like retinal detachment, iritis, uveitis, cataract, endophthalmitis and intraocular haemorrhage. Due to its net structured matrix, small molecules end up spreading homogeneously while bigger molecules spread in a more heterogeneous way, which leads to a thorough examination of the treatment before choosing therapeutic route (14). As other injection methods, we have intracameral injections that are aimed at diseases that affect the anterior part of the eye, since it is administered in the anterior chamber of the eye, avoiding the cornea, conjunctiva and blood aqueous barriers. This method is used mainly for the administration of antibiotics like vancomycin, moxifloxacin and cephalosporins to treat ocular infections and has as the major limitation the fact that needs a special preparation, leading to a high rigor regarding dose and sterilization, that if it is not met, can cause serious health complications for the patient (15). Another method in this category is the subconjunctival injections that have their administration site outside of the sclera which allows for the drug to reach the anterior segment, while avoiding ocular barriers like the cornea and the blood-aqueous barrier. Despite being barely invasive, it has as a disadvantage the fact that with this injection we can have a loss of drug through systemic circulation through the blood and lymphatic vessels in the subconjunctival area (15).

Systemic administration of drugs is also used to treat ocular diseases, mainly posterior ocular ones, since there are a lot of blood vessels that nourish the eye that can take those drugs to its target site and have the advantage of being administered by the patient, with high patient compliance and low economic costs. However, due to the blood retinal barrier and the blood-aqueous barrier, the dose that reaches the eye is between 1 to 5 per cent and because of that is not the most commonly used route of drug administration to eye conditions (5).

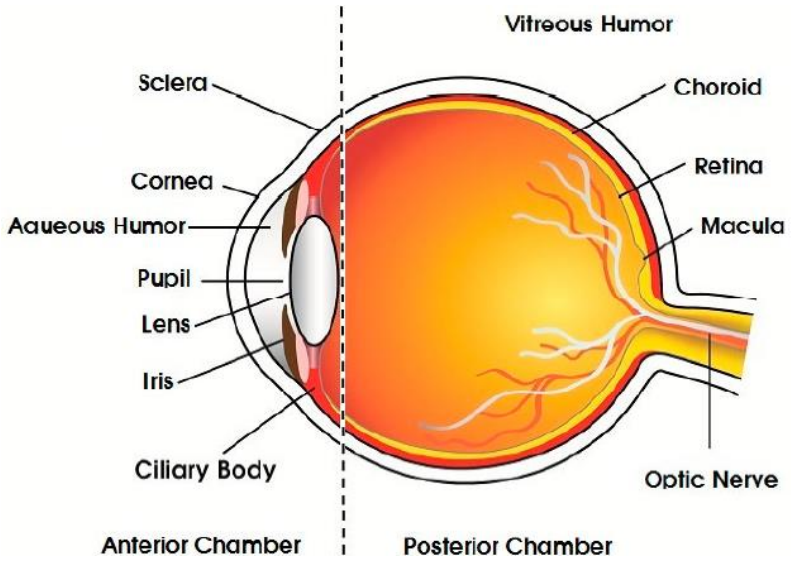

Figure 1 Anatomical Structure of the Eye adapted from Joseph M, Trinh HM, Cholkar K, Pal D, Mitra AK. Recent perspectives on the delivery of biologics to back of the eye. Expert Opin Drug Deliv. 2017;14(5):631–45. (16)

Methods and Materials

The methods used to write this monography were the search and analysis of numerous articles, books and other types of information from certificated and trustworthy platforms such as PubMed, Academic Google, Elsevier, ScienceDirect, among others.

Keywords used to search for these materials were: *nanoparticles, ocular drug delivery, anatomy of the eye, nanotechnology, nanomedicine, ocular therapies* and *ocular barriers*.

Results

Nanoparticles as Alternative Therapies Strategies

With all of these barriers, both the anatomical and the physiological ones, it becomes difficult to both achieve good bioavailability of drugs and patient compliance, which are the two major variables in ocular diseases treatment, with the conventional formulations (13,17). To overcome these obstacles, scientists and physicians have looked to nanoparticles as a way to transform traditional therapies because not only them offer many ways to change and shape more conventional treatments through the huge variety of materials used but also ensure better bioavailability of drugs without compromising patient compliance. In this part, we are going to dig into the innovations

in nanotechnology and nanomedicine that allowed us to take the next step in ocular drug delivery (18).

As it is well known, many ocular diseases have a chronic nature and due to that, many patients have the need to comply to a certain treatment for the rest of their lives and with all the limitations of the common ocular drug delivery systems or the invasive nature of injections can lead to problems in the long run. To tackle this, nanocarriers were developed to not only improve the permeability to ocular barriers but also to assure a durable and controlled release of the drug in the ocular environment, while protecting from enzyme's action. In the category of colloidal nanocarriers, we can include nanoparticles, nanowaffers, nanomicelles and microneedles (12). Because particles with dimensions above 10 (micrometers) can cause the foreign body sensation in the eye, nanocarriers usually have between 1 and 1000 (nanometeres).

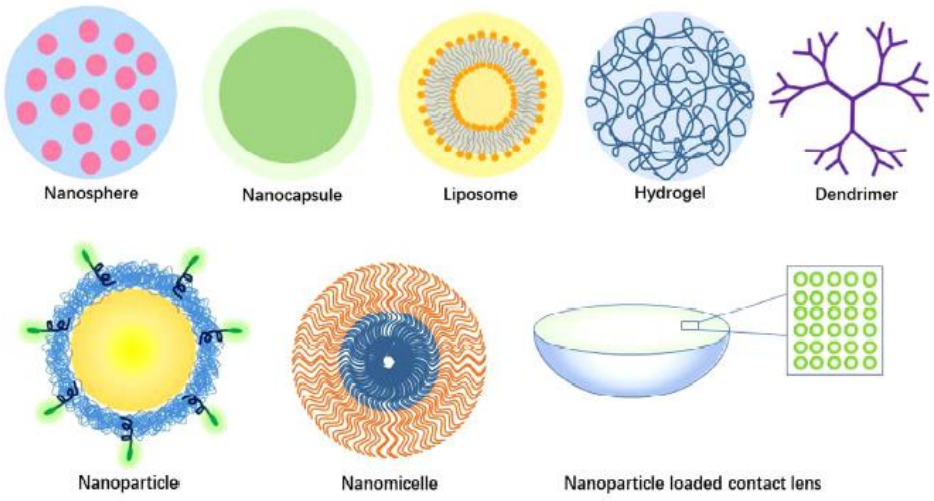

Figure 2 Nanoparticles for ocular drug delivery and hybrid nanomedicine technology. Some of the images reflect hybrids that were only briefly mentioned in this monography due to the primary focus on the nanoparticles mentioned below adapted from Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta Pharm Sin B [Internet]. 2017;7(3):281–91. Available from: http://dx.doi.org/10.1016/j.apsb.2016.09.001 (19)

- Nanomicelles: Nanomicelles form in an O/W solution and can transport medicines inside. When the concentration of polymers is above the CMC, these particles form with sizes ranging from 10 to 200 nanometers. Since the inside of the micelles is hydrophobic, it enables for hydrophobic drugs to better overcome eye barriers since the outside of the micelle is hydrophilic which will allow for a better penetration. This makes them optimal to be used in eye drops. Significant benefits nanomicelles showed over the years are related with a reduced drug degradation rate and toxicity and higher bioavailability of lipophilic drugs. This category can be further divided in two: surfactant nanomicelles and

polymeric nanomicelles (while surfactant nanomicelles are surfactant self-assembled molecules, polymeric nanomicelles have their origin in polymers) (12). Some drugs already being used as therapies are for example nanomicelles made of hydrogenated castor oil-40 and octoxynol-40 encapsulating Cyclosporine-A to treat dry eye disease in the anterior ocular segment. It has shown increased bioavailability than conventional formulations with the absence of adverse effects. In more recent years, scientists have created fixed combination of substances that lead to lower CMC (critical micelle concentration). With this, we can achieve nanomicelles with higher stability and this can lead to higher bioavailability of the drug. If these nanomicelles are created from polymers like PEG (polietilenoglicol) or PLA (Polylactic acid), they are called polymeric nanomicelles and have also showed great potential to deliver antibiotics, immunosuppressants or even DNA for gene therapy to both the anterior and posterior part of the eye (12). Another study took this technology a step further by designing a multi-layered nanomicelle, made with HCO-40 and OC40, with a hydrophilic interior that carried octreotide, aimed to treat proliferative diabetic retinopathy, inside a hydrophobic layer, being the outer layer hydrophilic. This was possible by assembling the different layers sequentially. These nanomicelles have increased loading characteristics, biocompatibility and stability, than can enable medicine to treat diseases specific from the posterior segment of the eye (20). A study that investigated a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer as a nanocarrier for curcumin administration in the eye, concluded that these nanomicelles enable an easier solubilization of drugs and has a higher storage capacity but also to have a better cell uptake and superior *in vivo* corneal permeation (21).

- Nanoparticles: Nanoparticles are a broader approach to nanocarriers and their size rages from 50 to 500 nm and they can either be deposited in the *cul-de-sac* or be applied on the cornea. Because they have a small size, they easily penetrate the eye through mechanisms of active transport or passive diffusion or get stuck in the membranes that make up the ocular globe. This leads to better bioavailability, released control of the medicine, without causing discomfort to the patient. Also, since we are able to change the charge of these nanoparticles, we can specifically develop them for a specific area of the eye, since the cornea and the conjunctiva are negatively charged, and cationic molecules are more easily retained. In this group, can be naoparticles

produced with polymers like PLGA (poly lactic glycolic acid) , PEG, PLA, PGA (polyglycolic acid), PCL (polycaprolactone), chitosan, albumin, hyaluronic acid, sodium alginate and gelatine (12) and also with lipids like SLNs (Solid Lipid Nanoparticles). A recent investigation with a PLGA nanoparticle encapsulating fluocinolone acetonide for posterior ocular inflammation administered through an intravitreal injection aimed to discover if these particles could overcome the problems associated with body clearance and a short half-life of fluocinolone acetonide in the organism. At the end of the study, it was possible to conclude that not only the PLGA nanoparticles increased the stability of the drug studied but also a controlled release of the substance over a period of 30 days, decreasing the need of continuous injections and the administration of high doses of fluocinolone acetonide (22). An experiment with a poly-(3-hydroxybutyrate-co-3-hydroxyvalerate) nanoparticle encapsulating hydrocortisone was tested as a topical administration route that would avoid the adverse effects of hydrocortisone while, at the same time, would penetrate to deeper layers of the cornea. After this investigation, it was concluded that this polymer could enable the administration of molecules that had more difficulty to pass through ocular barriers since results showed this drug delivery system lead to high bioavailability (23). In a study with another polymer, it was tested an etoposide loaded solid lipid nanoparticle to evaluate drug effective delivery to the posterior segment of the eye. In the end, after just 1 intravitreal injection, results showed that these particles continued to release etoposide over a period of 7 days without presenting adverse effects (2).

- Liposomes: Liposomes are another strategy to encapsulate drugs, showing more biocompatibility than polymer-based molecules. These molecules that range from 0.025 and 10 (micrometers), and that sometimes might be confused by micelles, have a lipid bilayer whereas micelles have a lipid monolayer with a fatty and a polar side (6). The big limitation of this technology is their poor stability, which can lead to poor bioavailability and storage stability. However, it can be combined with other techniques to improve its characteristics. One example of that is a study done in China with a liposome coated with PAMAM G3.0, (a third generation polyamidoamine dendritic polymers) that, among other characteristics, make it easy to target to a specific site. This is especially important in this essay because the aim is the posterior part of the eye, which makes crucial to have a formulation stable and with enough capacity of penetration to overcome all the ocular barriers. The drugs administered through

this route of administration were berberine hydrochloride and chrysophanol and it was concluded that with this formulation it was possible to reduce inflammation, better penetration and controlled release of both drugs (24). In another experiment, this one applying just the technology of liposomes with a HCl phosphatidylcholine liposome loaded with dorzolamide, aimed to make a comparison between this new formulation and the conventional one. In the end, the results lead them to conclude that the efficacy of the medicine and overall results were better due to the positive charged lipid bilayer of the liposome that makes it adhere better to the cornel layers, leading to a higher bioavailability (25).

- Dendrimers: Dendrimers are branch-shaped structures. They are synthesised from a variety of polymers and due to their characteristic shape, they can encapsulate drugs, characteristic that is potentialized with the surface functionalized groups, and form structures that easily dissolve in a homogeneous way, being highly soluble in water (6). In ocular therapy, dendrimers can be either conjugated with other molecules or encapsulate these molecules. Dendrimers are usually used with other techniques to achieve better results and a recent innovation is the use of electrospinning to create PAMAM dendritic nanofibers loaded with brimonidine tartrate, a drug used to treat glaucoma. Despite short term results showing no difference in efficacy comparing to conventional formulations, long term results showed a significant difference when this formulation was applied daily due to accumulation of dendrimer nanofibers in the anterior segment of the eye, which indicates an alternative to current therapeutic strategies (26).

- Microneedles: Steel microneedles are sharp shaped nanoparticles coated with drugs that penetrate in the eye in a very non-invasive way and can deliver medicines both to the anterior and the posterior part of the eye. This is a strategy to overcome the highly invasive route of ocular injections, especially intraventricular injections (12). In two recent studies, it was tested the possibility of injecting microneedles at different sites and depths to have a controlled release of drugs in specific parts of the eye. In one study, microneedles coated with Rhodamine B were injected in the sclera with the use of a microneedle pen and the result showed that this route of administration allows us to administered drugs near injections sites, making it easy to overcome ocular barriers. In this case, the injection site was in the sclera and being released there, drug

molecules were able to cross the sclera and reach the choroid within 6h (27). In another study, a different approach was taken by designing a microneedle pen with a detachable tip that would penetrate the eye and be left there to be biodegraded over time. The drugs used were FITC-dextran to examine the drug release and polyhexamethylene biguanide to examine the therapeutic applicability and results showed that this hybrid model, way less invasive than other injection strategies, had faster results than conventional therapies, while decreasing patient's discomfort (27).

- Nanowafers: Nanowafers are rectangular or disc like structures made of polymers that are nanoreservoirs loaded with drugs and that are applied on the eye, releasing the substance over time while creating a membrane that can help heal corneal damage. Since these polymers are biodegradable, nanowafers end up being eliminated overtime (6). In one trial, a nanowafer made of sodium methylcellulose and PDMS (polydimethylsiloxane) and filled with dexamethasone was administered to see what the result of this formulation in a therapy for ocular burn and desiccating stress could be. This ended up leading to a controlled release overtime of the drug and that could increase the efficacy of similar treatments due to the controlled release and increase of patients' compliance, since 1 administration of this modified drops would replace 4 administrations of the previous ones (28).

- Niosomes: Niosomes are also a colloidal system similar to liposomes and they are composed by a bilayer of self-assemble amphiphiles in an aqueous environment. They can take a shape of unilamellar or multilamellar vesicles. Despite being used in other therapies, it shows particular importance in ocular diseases due to its low toxicity and high adhesive properties. It has as a great characteristic the capacity of encapsulating both hydrophilic and lipophilic drugs with high biocompatibility and controlled release properties and, compared with liposomes, they have higher stability (29). A niosome prepared with Tween 60 and cholesterol and loaded with doxycycline hyclate was submitted to *in vitro* tests and also a Draize test that showed that these particles enabled a controlled release of the drug, could maintain its characteristics for 2 months when properly stored and did not cause any adverse effect when in contact with the eye (30). In other study, niosomes were coated with hyaluronic acid, a substance that is also present in the eye, more specifically in the aqueous body and vitreous body, could improve the bioavailability of tacrolimus, a drug used

in prevent corneal allograft rejection. Since hyaluronic acid has mucoadhesive properties, it was concluded that niosomes with this coating had better precorneal retention, increasing the bioavailability of the drug (31).

Discussion

According to the information gathered during the investigation to write this monography, it was concluded that nanoparticles will most certainly be the technology that will revolutionize ocular therapies and ocular drug delivery due to the rapid absorption and the capacity to easily overcome ocular barriers, which gives them the capacity to better reach both the anterior and the posterior part of the eye, ensuring better bioavailability and therapeutic results.

What concerns anterior ocular diseases, eye drops should keep on being the first choice for treatment due to its safety and high patient compliance and nanoparticles should be more and more included in this type of formulation in order to increase therapeutic efficacy. Nanoparticles will enable treatments with increased control in drug release, increased bioavailability in the eye, which is one of the aspects that continues to lack, and also by increased amount of drugs that can be delivered due to the synergy of different nanotechnologies, combining strengths from a wide variety of nanoparticles, creating hybrid formulations that have increased efficacy as we have seen in studies presented in this manuscript.

For the posterior ocular diseases, invasive methods continue to be the option that assures highest bioavailability and efficacy, but the problem of being highly invasive still remains troublesome as it leads to retinal detachment, haemorrhage and discomfort, that can later lead to patients giving up on treatments. Because of this, the future brings the challenge to find a different strategy to treat this group of diseases that does not present itself as invasive but that can assure the high efficacy that injections already bare.

Conclusion

The future of ocular diseases' treatments has its path drawn by today's problems such as the low bioavailability and patient compliance to therapies. Not only this, but recent studies have shown that ocular pathologies will affect more and more people as we advance in this technological area and diseases like cataract, glaucoma, wet and dry

age related macular degeneration, diabetic retinopathy and diabetic macular edema will have a bigger expression on the population (12). However, as we have seen in recent years, nanotechnology will most certainly by one of the pillars in this revolution due to the improvements it has shown to bring to conventional therapies.

Nanoparticles like nanomicelles, polymer nature nanoparticles, liposomes, microneedles, niosomes, dendrimers and nanowafers bring advantages such as higher bioavailability, lower toxicity and less side effects and a better penetration to deeper parts of the eye, being able to effectively delivery drugs for disease that affect posterior parts of the eye and avoiding the usage of invasive methods. Another strategy related with nanotechnology that will also bring an improvement to conventional formulation is the combination of different nanoparticles to form hybrid ones that gather in one nanoparticle the strengths of the other two.

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